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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,791	HEISKALA, MARJA	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,15-17,25-36,39-44,50 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,15-17,25-36,39-44,50 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *04/10/05* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group I, claims 1-5, 7, 15-17, 25-36, 39-44, 50, 52-55, species SEQ ID NO:2, without traverse, in paper of 01/24/05 is acknowledged and entered.

Applicant cancels claim 55.

After review and reconsideration, group I, 1-5, 7, 15-17, 25-36, 39-44, 50, 52-54 are further subjected to the following restriction:

RESTRICTION

Further Restriction of claims 1-5, 7, 15-17, 25-36, 39-44, 50, 52-54 to one of the following species is required under 35 U.S.C. § 121:

Claims 1-5, 7, 15-17, 25-36, 39-44, 50, 52-54 are generic to a plurality of disclosed patentably distinct species comprising any of the compounds, as cited in claim 17.

The species are distinct, each from the other because of the following reasons:

The compounds as cited in claim 17 have different characteristics and properties.

A telephone call was made to Guy Kevin Townsend, on 04/10/05 to request an oral election to the above restriction requirement, and results in the election of the species "alkylating agent".

Affirmation of this election must be made by applicant in responding to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if

one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Accordingly, claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54, species SEQ ID NO:2, alkylating agent, are examined in the instant application.

OBJECTION

In the Specification:

The specification is objected to, because it contains empty space, for example on page 14.

In the claims:

1. Claims 1-5, 7, 15-17, 25-38, 39-44, 50, 52-54 are objected to for the use of the language "RELP protein human Ig derived protein".

It is not clear how the human Ig is "derived" from the RELP protein.

2. Claims 1-5, 7, 15-17, 25-38, 39-44, 50, 52-54 are objected to for the use of the language "specified portion".

It is not clear which portion is specified, nor how it is specified.

3. Claims 1-5, 7, 15-17, 25-38, 39-44, 50 are objected to, because claim 1 uses the Marskush format, which is not appropriate, because only one sequence, SEQ ID NO:2, is recited in the selected group.

4. Claim 5 is objected to for the use of the language "activity". It is not clear what type of activity is referred to.

REJECTION UNDER 35 USC 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 52-54 are rejected under 35 USC 101 because the claims are directed to non-statutory subject matter.

The RELP protein human Ig derived protein as claimed has the same characteristics and utility as a protein found naturally and therefore do not constitute patentable subject matter. In the absence of the hand of man, the naturally occurring polypeptide is considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Amendment of the claims to recite " an isolated RELP protein human Ig derived protein" is suggested to overcome this rejection.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 26-27, 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 26-27 are indefinite for lacking antecedent basis, for the use of the language "one human Ig derived protein fragment according to claim 1", because the language "fragment" is not recited in claim 1.

2. Claim 50 is indefinite, because the method recited in claim 50 lacks an essential step of expressing and recovering the human Ig derived protein, or specified portion or variant.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54 are drawn to:

1) An isolated "RELP protein" "human Ig derived protein", comprising at least one human variable region, wherein said human Ig derived protein or specified portion or "variant" specifically binds to at least "one epitope comprising at least 1-3", to the entire amino acid sequence of SEQ ID NO:2, or a medical device, a formulation or an article of manufacture, comprising said human Ig derived protein. Said human Ig derived protein, or specified portion or variant could bind "RELP protein" with an affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M . Said human Ig derived protein, or specified portion or variant

could substantially neutralize at least one activity of "at least one RELP protein" . Said RELP protein human Ig derived protein, or specified portion or variant could be encoded by a nucleic acid that encodes a RELP Ig derived protein according to claim 1 (claims 1-5, 7, 15-17, 25, 29-36, 39-43, 50),

2) A human immunoglobulin light chain or heavy chain RELP protein or portion thereof, comprising at least one portion of a variable region comprising "at least one human Ig derived protein" fragment according to claim 1 (claims 26-27).

3) A "human Ig derived protein," or specified portion, or "variant" thereof, which binds to the same epitope or antigenic region as a RELP protein "human Ig derived protein", or specified portion, or "variant" according to claim 1 (claim 28),

4) A method for preparing a formulation of at least one RELP protein "human Ig derived protein" or specified portion or "variant "(claim 44),

5) An "RELP" protein "human Ig derived protein" or specified portion or "variant" that binds "RELP protein" with an affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M (claims 52-54).

The specification discloses that "Ig derived protein" is intended to encompass Ig derived proteins, fragments, "variants" thereof, and mimetics that mimic the structure and/or function of an antibody (p.13, lines 27-30).

It is noted that in view of the definition of "Ig derived protein" in the specification, claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54 encompass "variants" or mimetics of the wild type human Ig derived protein (i.e human antibody specific for SEQ ID NO:2), wherein the structure of said variants or mimetics is not disclosed.

It is further noted that the "at least 1-3 epitopes" of SEQ ID NO:2, to which the claimed human Ig derived protein binds, do not necessarily have to be specific for SEQ ID NO:2, and could be shared by unknown antigen sequences. In other words, the antigen bound by the claimed human Ig derived protein needs only to share at least 1-3 epitopes with SEQ ID NO:2, because said epitopes could be as small as a few amino acids, and is not necessarily unique for SEQ ID NO:2. Thus the antigen, to which the claimed human Ig derived protein binds, encompasses unknown sequences, with unknown structure.

It is also noted that the recited "RELP protein", without being specified as SEQ ID NO:2 encompasses variants of the RELP protein of SEQ ID NO:2, with unknown structure.

A. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that A [a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials.Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

In the instant application, the specification describes only a single human Immunoglobulin that binds to the RELP protein of SEQ ID NO:2. Therefore, it necessarily fails to describe a "representative number" of species of variants of the

human Ig derived protein. In addition the specification fails to describe "structural features common to members of the genus, which features constitute a substantial portion of the genus". Thus the specification fails to describe an RELP protein, by the example set out in Lilly.

Moreover, another recent court case, Rochester, applies as well to the instant application (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004). The court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that although an antibody inhibitor of the RELP protein of SEQ ID NO:2 is disclosed, one cannot predict what mimetics of the human Ig derived protein, especially in view that three dimensional structure of antibody inhibitor of the RELP protein of SEQ ID NO:2 is not even disclosed in the specification or known in the art.

Thus one would reasonably conclude that Applicant did not possess a genus of variants or mimetics of the human Ig derived protein at the time the invention was made.

B. Further, the following teaching of the court as set out in Noelle clearly applies to the instant unknown antigen sharing a non-specific epitope with SEQ ID NO:2, to which the RELP protein human Ig derived protein binds, or to the claimed "RELP protein" variants to which the RELP protein human Ig derived protein binds, without specifying that said RELP protein consists of SEQ ID NO:2. The court teaches as

follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

In the instant application, the specification only discloses a single polypeptide of SEQ ID NO:2 to which the claimed RELP human Ig derived protein binds. The instant application does not however describe a genus of antigens sharing an

epitope with SEQ ID NO:2, to which the claimed variant of the RELP human Ig derived protein binds, or a genus of "RELP protein" variants to which the RELP protein human Ig derived protein binds. Since the instant application does not describe the genus of antigens to which the claimed variant of the RELP human Ig derived protein binds, or a genus of "RELP protein" variants to which the RELP protein human Ig derived protein binds, the instant application cannot claim the genus form of polypeptides sharing an epitope with SEQ ID NO:2, or of variants of the RELP protein of SEQ ID NO:2, by simply describing the RELP protein of SEQ ID NO:2. Thus the specification fails to describe a genus of polypeptides sharing an epitope with SEQ ID NO:2, to which the claimed RELP human Ig derived protein binds, or a genus of RELP variants to which the RELP protein human Ig derived protein binds, by the test set out in the example of Noelle.

One of skill in the art would conclude that Applicant was not in possession of the genus of antigens or RELP variants to which the claimed RELP human Ig derived protein binds at the time the invention was made.

Thus, the specification does not provide an adequate written description of a variant or mimetic of RELP human Ig derived protein, or an antigen that shares 1-3 epitopes with SEQ ID NO:2, or a RELP variant, to which the claimed RELP human Ig derived protein binds, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54 are rejected under 35 USC 112, first paragraph. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

1. Claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54 are rejected under 35 USC 112, first paragraph, because while being reasonably enabled for a human antibody that specifically binds to the RELP protein of SEQ ID NO:2, **the specification is not reasonably enabled for a variant or mimetics of an RELP protein human Ig derived protein, or a variant of the RELP protein of SEQ ID NO:2.**

Claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-54 are drawn to:

1) An isolated "RELP protein" "human Ig derived protein", comprising at least one human variable region, wherein said human Ig derived protein or specified portion or "variant" specifically binds to at least "one epitope comprising at least 1-3", to the entire amino acid sequence of SEQ ID NO:2, or a medical device, a formulation or an article of manufacture, comprising said human Ig derived protein. Said human Ig derived protein, or specified portion or variant could bind "RELP protein" with an affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M . Said human Ig derived protein, or specified portion or variant could substantially neutralize at least one activity of "at least one RELP protein" . Said RELP protein human Ig derived protein, or specified portion or variant could be encoded by a nucleic acid that encodes a RELP Ig derived protein according to claim 1 (claims 1-5, 7, 15-17, 25, 29-36, 39-43, 50),

2) A human immunoglobulin light chain or heavy chain RELP protein or portion thereof, comprising at least one portion of a variable region comprising at least one human Ig derived protein fragment according to claim 1 (claims 26-27).

3) A human Ig derived protein, or specified portion, or "variant" thereof, which binds to the same epitope or antigenic region as a RELP protein human Ig derived protein, or specified portion, or "variant" according to claim 1 (claim 28),

4) A method for preparing a formulation of at least one RELP protein human Ig derived protein or specified portion or "variant "(claim 44),

5) An "RELP" protein human Ig derived protein or specified portion or "variant" that binds "RELP" protein with an affinity of at least M (claims 52-54).

The specification discloses that "Ig derived protein" is intended to encompass Ig derived proteins, fragments, "variants" thereof, and mimetics that mimic the structure and/or function of an antibody (p.13, lines 27-30).

The specification discloses that as used herein, "RELP Ig derived protein" decreases, blocks, inhibits, abrogates interferes with RELP protein activity, binding or RELP protein receptor activity or binding in vitro or in vivo (p.5, lines 1-5).

It is noted that in view of the definition of "Ig derived protein" in the specification, claims 1-5, 7, 15-17, 25-36, 39-44, 50 and 52-55 encompass "variants" or mimetics of the human Ig derived protein, wherein the structure of said variants or mimetics is not disclosed.

It is further noted that the "at least 1-3 epitopes" of SEQ ID NO:2, to which the claimed human Ig derived protein binds, do not necessarily have to be specific for SEQ

ID NO:2, and could be shared by unknown antigen sequences. In other words, the antigen bound by the claimed human Ig derived protein needs only to share at least 1-3 epitopes with SEQ ID NO:2, because said epitopes could be as small as a few amino acids, and is not necessarily unique for SEQ ID NO:2. Thus the antigen, to which the claimed human Ig derived protein binds, encompasses unknown sequences, with unknown structure.

It is also noted that the recited "RELP protein", without being specified as SEQ ID NO:2, encompasses variants of the RELP protein of SEQ ID NO:2, with unknown structure.

A. Applicant has not taught how to make variants or mimetics of the wild type RELP human Ig derived protein, or variants of the RELP protein of SEQ ID NO:2, such that they would function as claimed.

One cannot extrapolate the teaching in the specification to the scope of the claims, because one cannot predict that 1) the claimed variant or mimetic of RELP human Ig derived protein would be have the same characteristics and properties of an antibody specific for SEQ ID NO:2 and 2) the claimed variants of SEQ ID NO:2 would have the same characteristics and properties of SEQ ID NO:2..

It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity, characteristics and three dimensional structure of a protein, and that 3- dimensional folding of the native molecule, however, is of significant

importance in an antibody response. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The 3- dimensional folding of the native molecule however is of significant importance in an antibody response, because epitopes of an antibody could be linear and/or conformational. For example, Roger, I et al, 1988, Bioscience Reports, 8(4): 359-368, teach that several epitopes of p85 glycoprotein are conformational determinants and are destroyed by reduction of said glycoprotein (abstract). The references thus demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the characteristics or three- dimensional structure of a protein, and consequently the binding and characteristics of the antibodies specific for said protein. Similarly, the sensitivity of proteins to alterations of even a single amino acid in a

sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). In addition, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54).

The references thus demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification of an antibody will often dramatically affect the characteristics and binding properties of the antibody. Similarly, even a single amino acid substitution or what appears to be an inconsequential chemical modification of a protein will often dramatically affect the characteristics and three- dimensional structure of the protein, and consequently the binding and characteristics of the antibodies specific for said protein.

In view of the above, it would be undue experimentation for one of skill in the art to make and use the claimed variants or mimetics.

B. Further, it is noted that the claimed "portion" or "fragment "of an RELP protein human Ig derived protein, as claimed in claims 26-27, does not necessarily bind to the antigen of SEQ ID NO:2. For example, a portion or fragment could be a single amino acid or a few amino acids of the claimed RELP protein human Ig derived protein.

In view of the above, one would not know how to use the claimed portion or fragment, and it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph, **Claims 39-42 are still rejected under 35 USC 112, first paragraph, because claims 39-43 encompass an RELP protein human Ig derived protein that binds to SEQ ID NO:2 for use in in vivo therapy, as contemplated.**

Claims 39-43 are drawn to an article of manufacture for "human pharmaceutical use", comprising packaging material and a container comprising a solution or a lyophilized form of at least one RELP protein human Ig derived protein, or specified portion or variant according to claim 1.

It is noted that "for human pharmaceutical use" encompasses in vivo use for treating diseases.

The specification contemplates the use of the claimed RELP Ig derived protein for treating at least one malignant disease in a patient (p.46-48, Therapeutic applications).

One cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known that the art of anticancer drug discovery for cancer

therapy is highly unpredictable. White et al, 2001, Ann Rev Med, 52: 125-145, teach that for a successful immunotherapy, besides the specificity of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). In view of the above, it is unpredictable that the antigen of SEQ ID NO:2 is suitable for antibody targeting.

In addition, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction

by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-5, 7, 26-28, 50, 52-54 are rejected under 35 USC 103(a) as being obvious over WO 96/39541-A1, or WO2001/49716-A2, in view of Burnett, K et al, In: Human hybridoma and monoclonal antibodies, Engleman et al, eds, Plenum Press, New York, 1985, pages 114-115, and WO 82/01461.

Claims 1-5, 7, 26-28, 50, 52-54 are drawn to:

1) An isolated RELP protein human Ig derived protein, comprising at least one human variable region, wherein said human Ig derived protein or specified portion

specifically binds to at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:2 (claim 1). At least one RELP human Ig derived protein or specified portion of claim 1 produced by a method comprising providing a host cell, transgenic animal, transgenic plant or plant cell capable of expressing said human Ig derived protein, or specified portion (claim 50).

2) Said human Ig derived protein, or specified portion could bind RELP protein with an affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M (claims 2-4).

3) Said human Ig derived protein, or specified portion could substantially neutralize at least one activity of at least one RELP protein (claim 5).

4) Said RELP protein human Ig derived protein, or specified portion could be encoded by a nucleic acid that encodes a RELP Ig derived protein according to claim 1 (claim 7).

5) A human immunoglobulin light chain or heavy chain RELP protein or portion thereof, comprising at least one portion of a variable region comprising at least one human Ig derived protein fragment according to claim 1 (claims 26-27).

6) A human Ig derived protein, or specified portion thereof, which binds to the same epitope or antigenic region as a RELP protein human Ig derived protein, or specified portion, according to claim 1 (claim 28),

7) An RELP protein human Ig derived protein or specified portion that binds RELP protein with an affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M (claims 52-54).

It is noted that the claimed RELP protein human Ig derived protein encompasses an antibody that binds specifically to SEQ ID NO:2.

It is further noted that a human Ig derived protein, that could substantially neutralize at least one activity of at least one RELP protein encompasses an antagonist antibody specific for SEQ ID NO:2.

In addition, it is noted that claim 50 is a product by process and is treated as the product per se, i.e one RELP protein human Ig derived protein or specified portion thereof.

WO 96/39541-A1 teaches a human colon specific protein, and antibodies and antagonists specific for the protein for the diagnosis and treatment of colon cancers (abstract, p. 14, last two paragraphs to p.17, and claims 9-12).

The protein taught by WO 96/39541-A1 is 100% similar to the full length sequence of SEQ ID NO:2, as shown in MPSRCH sequence similarity search (MPSRCH search report, 2005, us-10-099-791e-2.rag, pages 1-2).

Thus the antibodies and antagonist antibodies taught by WO 96/39541-A1 seem to be the same as the Ig derived protein to SEQ ID NO:2 for use in making the claimed human Ig derived protein to SEQ ID NO:2.

WO 96/39541-A1 does not teach a "human" antibody, wherein said antibody could have a binding affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M. WO 96/39541-A1 does not teach that the RELP protein human Ig derived protein neutralizes at least one activity of at least one RELP protein. WO 96/39541-A1 does not teach that the RELP protein human Ig derived protein, or specified portion is encoded by a nucleic acid that encodes a RELP Ig derived protein. WO 96/39541-A1 does not teach a human Ig derived protein, or specified portion thereof, which binds to the same epitope or

antigenic region as a RELP protein human Ig derived protein, or specified portion, specific for SEQ ID NO:2 of claim 1.

WO2001/49716-A2 teaches a colon tumor associated protein, the polynucleotides that encode it, and antibodies or antagonist thereof, which can be used for diagnosis of the presence of said protein or for down regulating the expression and activity of the protein (Summary on pages 2-6, Binding agents on pages 75-80, and Examples 1-5, summary in the MPSRCH search report, 2005, us-10-099-791e-2.rag, pages 4-5).

The protein taught by WO2001/49716-A2 is 100% similar to the full length sequence of SEQ ID NO:2, as shown in MPSRCH sequence similarity search (MPSRCH search report, 2005, us-10-099-791e-2.rag, pages 4-5).

Thus the antibodies and antagonist antibodies taught by WO2001/49716-A2 seem to be the same as the Ig derived protein to SEQ ID NO:2 for use in making the claimed human Ig derived protein to SEQ ID NO:2.

Burnett, K et al teach human antibodies to defined antigens for diagnostic and therapeutic use.

WO 82/01461 teaches how to make human antibodies, and production of heavy and light chains by the hybridoma (abstract and claims 1-9).

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to obtain the antibodies or antagonist antibodies taught by WO 96/39541-A1, or WO2001/49716-A2, which seem to be the same as the Ig derived protein to SEQ ID NO:2 for use in making the claimed human Ig derived protein

to SEQ ID NO:2, and to make human antibodies, or antigen binding fragments thereof, from the antibodies or antagonist antibodies taught by the art, using the method taught by WO 82/01461. The motivation is for diagnostic and therapeutic use, as taught by Burnett et al, wherein unwanted immunogenicity produced in the human patients by antibodies from a different species, such as from mice would be avoided.

One would have expected that the human antibody produced by the combined art would have the same properties and characteristics as the claimed human Ig derived protein to SEQ ID NO:2, such as having binding affinity of at least 10^{-9} M, 10^{-11} M, or 10^{-11}M, because the claimed human Ig derived protein to SEQ ID NO:2 is produced by routine method known from the art, using the same non-human antibody as that of the art. One would have expected that the human antagonist antibody produced by the combined art would neutralize at least one activity of at least one RELP protein, because neutralizing the activity of the target antigen is the property of antagonist antibodies, and because the RELP protein of the claimed invention is the same the protein taught by the art. One would have expected that the human antibody produced by the combined art would be encoded by a nucleic acid encoding the art human antibody, which is expected to be the same as the nucleic acid encoding the claimed human RELP Ig protein to SEQ ID NO:2, because the human antibody produced by the combined art is expected to have the same properties and characteristics as the claimed human Ig derived protein to SEQ ID NO:2, and because no particular, specific nucleic acid encoding the claimed human RELP Ig protein to SEQ ID NO:2 is recited in claim 7. One would have expected that the human antibody produced by the combined

art would bind to the same epitope or antigenic region as a RELP protein human Ig derived protein, or specified portion, specific for SEQ ID NO:2, because the target antigen of the human antibody produced by the combined art is exactly the same as SEQ ID NO:2 of the claimed invention.

One of ordinary skill in the art would have been motivated to make a human antibody specific for SEQ ID NO:2 with a reasonable expectation of success.

2. Claims 15-16, 29-36, 44 are rejected under 35 USC 103(a) as being obvious over WO 96/39541-A1, or WO2001/49716-A2, in view of Burnett, K et al, In: Human hybridoma and monoclonal antibodies, Engleman et al, eds, Plenum Press, New York, 1985, pages 114-115, and WO 82/01461, supra, and further in view of Johnstone and Thorpe (Immunochemistry in Practice, 2nd Ed., 1987, Blackwell Scientific Publications, Oxford, pages 49-50), US 5,834,422, US 6,440,930, and US 4,849,227.

Claims 15, 16 are drawn to :

A composition comprising at least one RELP protein human Ig derived protein, or specified portion or variant of claim 1 and a carrier or diluent (claims 15-16).

Claims 29-36 are drawn to:

A formulation comprising at least one RELP protein human Ig derived protein, or specified portion or variant of claim 1, in sterile water, sterile buffered water, or one of the preservatives recited in claim 29 (claim 29). Said formulation could be in lyophilized form in a first container, and an optional second container comprising sterile water. sterile buffered water, or one of the preservative recited in claim 33 (claim 33).

The concentration of RELP protein human Ig derived protein in claim 29 or 33 is about 0.1 mg/ml to about 100 mg/ml, or about 0.1 mg/ml to about 500 mg/ml (claims 30, 34).

Said formulation further comprises an isotonicity agent, or a physiologically acceptable carrier (claims 31-32, 35-36).

Claim 44 is drawn to:

A method for preparing a formulation of at least one RELP protein human Ig derived protein or specified portion, comprising admixing at least one of said human Ig derived protein, or specified portion of claim 1 in at least one buffer containing saline or salt (claim 44).

It is noted that a pharmaceutically acceptable carrier could be interpreted as any type of carrier, such as buffer, provided that it is pharmaceutically acceptable.

The teaching of WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 has been set forth above.

WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 do not teach a pharmaceutically acceptable carrier or diluent or sterile buffered water. WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 do not teach that the concentration of RELP protein human Ig derived protein is about 0.1 mg/ml to about 100 mg/ml, or about 0.1 mg/ml to about 500 mg/ml. WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 do not teach an isotonicity agent.

Johnstone and Thorpe teach that compositions of antibodies are stored in phosphate buffer saline, which is considered to be an acceptable carrier for storage of antibodies, because Johnstone and Thorpe teach that antibodies could be damaged, even though antibodies are robust proteins, and that antibodies are happiest in neutral isotonic buffers such as PBS (p.50, first paragraph).

US 5,834,422 teaches a combination of an isotonicity agent, such as a solution containing chloride and glycerol and a buffer for formulating an insulin composition (claim 2).

US 6,440,930, and US 4,849,227 teach various preservatives for protein formulations and storage stability.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate the human antibody taught by WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 in buffer, such as phosphate buffer saline (PBS), because of the following reasons: 1) Johnstone and Thorpe teach that compositions of antibodies are stored in phosphate buffer saline, which is considered to be an acceptable carrier for storage of antibodies, because Johnstone and Thorpe teach that antibodies could be damaged, even though antibodies are robust proteins, and that antibodies are happiest in neutral isotonic buffers such as PBS (p.50, first paragraph), and 2) Antibodies are proteins and it was conventional to store proteins in phosphate buffer saline. It would have been obvious to add to the human antibody taught by the combined art any of the preservative taught by US 6,440,930, and US 4,849,227 to stabilize the antibody. Further, it would have been

obvious to further add to the human antibody taught by WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 an isotonicity agent, such as a solution containing chloride and glycerol, as taught by US 5,834,422 to stabilize the protein. It would have been obvious to formulate the human antibody taught by WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 in lyophilized form and stored in a first container, and an optional second container comprising sterile buffered water, because lyophilization of proteins is a convenient and routine method for storing a protein in a commercial container.

Concerning the recited concentration cited in claims 30, 34, to determine optimum concentrations of reactants is within the level of one of ordinary skill in the art (In re Kronig).

One of ordinary skill would have been motivated to do so in order to develop compositions suitable for storage. One of ordinary skill in the art would have been motivated to make a human antibody specific for SEQ ID NO:2, store it a buffer, or a preservative, and an isotonic agent, or lyophilize it for storage in a container, with a reasonable expectation of success.

3. Claim 17 is rejected under 35 USC 103(a) as being obvious over WO 96/39541-A1, or WO2001/49716-A2, in view of Burnett, K et al, In: Human hybridoma and monoclonal antibodies, Engleman et al, eds, Plenum Press, New York, 1985, pages 114-115, and WO 82/01461, further in view of Johnstone and Thorpe, supra, and further in view of US 6,123,939.

Claim 17 is drawn to: A composition comprising at least one RELP protein human Ig derived protein, or specified portion or variant of claim 1 and a carrier or diluent. Said composition further comprises an alkylating agent.

The teaching of WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 and Johnstone and Thorpe has been set forth above.

WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, WO 82/01461, and Johnstone and Thorpe do not teach an alkylating agent.

US 6,123,939 teaches a combination of an antineoplastic drug such as an alkylating agent, most preferably cisplastin, and an antibody for treating cancer. US 6,123,939 further teaches that the combination has a synergistic effect.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the human antibody taught by WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461, and Johnstone and Thorpe with an antineoplastic drug such as an alkylating agent, as taught by US 6,123,939, because the alkylating agent is an antineoplastic drug, and would have a synergistic effect with the antibody in killing cancer cells, as taught by US 6,123,939.

One of ordinary skill in the art would have been motivated to combine the human antibody with an akylating agent, with a reasonable expectation of success.

4. Claims 25, 39-43 are rejected under 35 USC 103(a) as being obvious over WO 96/39541-A1, or WO2001/49716-A2, in view of Burnett, K et al, In: Human hybridoma

and monoclonal antibodies, Engleman et al, eds, Plenum Press, New York, 1985, pages 114-115, and WO 82/01461, supra, and further in view of US 5,117,981, US 5,533,993, US 5,200,178, US 4,944,942, US 6,794,374 and US 6,165,975.

Claim 25 is drawn to:

A medical device comprising at least one RELP protein human Ig derived protein that binds to SEQ ID NO:2, wherein said device is suitable to contacting or administrating said RELP protein human Ig derived protein by intravenous mode, or any other route of administration recited in claim 25 (claim 25).

Claims 39-43 are drawn to:

An article of manufacture for human pharmaceutical use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one RELP protein human Ig derived protein, or specified portion thereof according to claim 1. Said container could be a glass or plastic container having a stopper for multi-use administration. Said container is a blister pack, capable of being punctured and used in intravenous administration, or any other route of administration recited in claim 41, or a delivery device or system for use in intravenous, or any other route of administration recited in claim 42, or 43. Said container could be a component of an injector or pen-injector device (claims 39-43).

It is noted that claims 39-43 recite the claimed RELP protein human Ig derived protein in solution or lyophilized "for human pharmaceutical use". However, this limitation is viewed as a recitation of intended use and therefore is not given patentable

weight in comparing the claims with the prior art. Claims 39-43 read on the ingredient per se, which is RELP protein human Ig derived protein in solution or lyophilized.

The teaching of WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 has been set forth above.

WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 do not teach a medical device suitable for intravenous injection, or any other route of administration as recited in claim 25, or a glass or plastic container having a stopper for multi-use administration. WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 do not teach a blister pack, or an injector for intravenous administration, or any other route of administration as recited in claim 41, 42, or 43.

US 5,117,981 teaches a kit for preparing and dressing an intravenous catheter site comprising a tray in the form of a blister pack (claim 1).

US 5,533,993 teaches a medication injector for use intravenous administration (claim 1).

US 5,200,178, US 4,944,942, US 6,794,374 and US 6,165,975 teach various routes of administration.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate the human antibody taught by WO 96/39541-A1, or WO2001/49716-A2, Burnett, K et al, Engleman et al, and WO 82/01461 in solution or lyophilized, because these are conventional form for storage of proteins for commercial purpose. It would have been obvious to formulate said antibody in a glass

or plastic container having a stopper for multi-use administration for commercial purpose. It would have been obvious to formulate said antibody in a medical device, for commercial purpose, such as a blister pack for intravenous administration, as taught by US 5,117,981, because the blister pack is commonly used for intravenous injection. It would have been obvious to store said antibody in a container comprising an injector for intravenous administration, as taught by US 5,533,993, for commercial purpose. . It would have been obvious to replace intravenous route of administration with any other route of administration as taught by US 5,200,178, US 4,944,942, US 6,794,374 and US 6,165,975, because these are commonly used method for delivery therapeutic compounds.

One of ordinary skill would have been motivated to do so, with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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MINH TAM DAVIS

April 13, 2005

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